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Phase II Trial for Intraperitoneal Cisplatin Plus Intravenous Sodium Thiosulphate in Advanced Ovarian Carcinoma Patients with Minimal Residual Disease After Cisplatin-based Chemotherapy—a Phase II Study of the EORTC Gynaecological Cancer Cooperative Group

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On the basis of its efficacy against ovarian carcinoma and its safe peritoneal administration, cisplatin administered by the intraperitoneal route was studied in a phase II multicentric trial. 34 patients with good performance status and residual disease less than 1 cm were treated with a 90 mg/m² dose (60 mg/m² at first cycle), administered in the abdominal cavity every 3 weeks for at least four cycles. In case of haematological or renal toxicity, intravenous sodium thiosulphate was perfused simultaneously with intraperitoneal cisplatin with protective intent. 25 patients were evaluable for response: 3 patients had pathological complete response and 1 patient had a microscopic disease (16% response rate in evaluable patients). Systemic toxicity was mild, and sodium thiosulphate clearly protected against leucopenia (6 patients) and renal toxicity (8 patients). Local side-effects were evaluable in 34 patients with 2 cases of infectious peritonitis, 1 of wound infection and 2 of haemorrhage. Of the 147 evaluable chemotherapy cycles, nine resulted in partial and one in total inflow obstruction, for which 4 patients needed surgical procedures for catheter-related complications, and 1 patient died of acute abdominal complications after such a procedure. We conclude that 90 mg/m² intraperitoneal cisplatin has activity in pretreated patients with minimal residual disease, and that thiosulphate protects against haematological and renal toxicities. Only a randomised study can demonstrate a true benefit, which will have to be balanced with the toxicity of intraperitoneal drug administration.
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INTRODUCTION

IN PATIENTS with advanced ovarian cancer, promising results have been observed by intensive chemotherapy with cisplatin-containing combinations in conjunction with surgical "debulking" procedures. Pathologically documented, complete remission rates range from 25 to 40%, and the survival rate for this group of patients is 65% at 5 years and 45% at 7 years [1, 2]. However, in about 15–20% of the patients, minimal residual disease persists, in spite of continued systemic treatment. Minimal residual disease represents that group of patients who have only small tumours (≤1 cm) or microscopic disease at the time of second-look laparotomy. In these patients, local intracavitary application of cytotoxic agents offers a further therapeutic perspective, as was shown in preliminary studies [3, 4].

Pharmacokinetic studies have established that for many drugs, there is a pharmacological advantage to be gained by using the intraperitoneal route [5]. Cisplatin is probably the most important drug in the chemotherapy regimens for ovarian cancer, and intraperitoneal application has led to complete responses [6–10]. In the Netherlands Cancer Institute Study, all responders were treated at a 60 mg/m² dose level. Furthermore, Howell [10] showed a definite decrease of cisplatin-induced renal toxicity by intravenous administration of the neutralising agent sodium thiosulphate. A protective effect on the degree of myelosuppression by intravenous thiosulphate was observed by ten Bokkel Huinink [9].

The purpose of this trial was to study the antitumour effect and toxicity of cisplatin administrated intraperitoneally in the setting of a multicentre trial, and to evaluate the role of sodium thiosulphate as a protective agent against renal toxicity and myelosuppression for patients with minimal residual disease.

MATERIALS AND METHODS

Only EORTC collaborative centres with a staff trained to use intraperitoneal administration of drugs were allowed to enter patients. Patients were registered at the EORTC Data Center.

Table 1. Dose modification according to haematological toxicity

WBC nadir ($\times 10^9$)	Platelet nadir ($\times 10^9$)	Cisplatin dose	Sodium thiosulphate
>3.0	>75	100%*	No
1.0–3.0	20–75	100%†	Yes
<1.0	<20	100%‡	Yes

*After the first course, cisplatin was escalated from 60 to 90 mg/m² if no toxicity was observed. †If toxicity was observed during the first cycle with 60 mg/m² of cisplatin no dose escalation was performed but thiosulphate was added to that same dose. ‡If this occurred at the dose level of 90 mg/m² plus sodium thiosulphate, dose reduction of cisplatin to 60 mg/m² plus thiosulphate was necessary.

Eligibility requirements

Criteria for inclusion were histologically-verified ovarian carcinoma stage III and IV, patients with minimal residual disease (tumour diameter ≤1 cm) and previous treatment with intravenous cisplatin.

Criteria for exclusion were WHO performance status >2, age >75 years, life expectancy <3 months, creatinine clearance <40 ml/min, WBC $<3 \times 10^9$/l or platelet count $<100 \times 10^9$/l, second malignant disease, staging procedure carried out more than 8 weeks prior to protocol treatment and inadequate fluid distribution in the abdomen due to catheter position or adhesions.

Protocol

A Tenchkoff catheter was inserted into the peritoneal cavity by laparotomy or by laparoscopy. Port-A-Cath systems were handled according to manufacturers' guidelines (employing aseptic technique when accessing the system, use of Port-a-cath needle, flushed with 20 ml saline after infusion, a pressure of 40 psi not exceeded when administering fluid through the system). If no Port-A-Cath systems were used, postoperative management of the Tenchkoff catheter consisted of a constant drip of 20 ml/h of dialysis fluid, maintained for 6–7 days through the Tenchkhoff catheter. Thereafter, the system was closed after instillation of 10 ml saline solution with 2500 U of heparin. Once every 3 weeks, this latter procedure was repeated after administration of the cisplatin.

Intraperitoneal chemotherapy consisted of cisplatin diluted in 2 l of dialysis fluid, instilled via a Tenckhoff catheter and drained after 4 h. The dose of cisplatin was 60 mg/m² at the first cycle. If no toxicity occurred after the first intraperitoneal cisplatin administration, the next cycle was started 3 weeks later using a cisplatin dose of 90 mg/m² (Table 1). No further increase in dose followed thereafter. If haematological (Table 1) or renal toxicity (defined as a 25% increase in basal creatinine level) occurred, the same dose of cisplatin was repeated in the next cycle, with the addition of intravenous sodium thiosulphate: 3 g/m² as a bolus started concomitantly with intraperitoneal cisplatin, and followed by a 6-h continuous infusion of 2 g/m²/h. The treatment was repeated every 3 weeks for at least four cycles as long as there was no clinical or X-ray evidence of disease progression. Patients were monitored with weekly blood counts and electrolyte dosages. Physical examination, serum chemistries, ascites cytology and WHO toxicity rating were performed at each cycle of intraperitoneal chemotherapy. Every three cycles of chemotherapy, the intraperitoneal fluid distribution was assessed by a computer tomography (CT) scan of the abdominal space after instillation of contrast material through the catheter. At the end of six courses of treatment, re-evaluation was carried out: in case of negative findings at examination and CT scan evaluation, with negative cytology of aspirated ascites fluid, a peritoneoscopy was performed (optional). If peritoneoscopy was negative or not performed, a restaging laparotomy was indicated for evaluation: description and biopsies of residual tumours, washing with saline solution for cytology and blind biopsies of peritoneum and diaphragm. Only complete responses were considered as a response. Pathological complete response (PCR) was defined as the disappearance of all macroscopical and microscopical disease at laparotomy, with negative biopsies and negative intraperitoneal washing.

Statistical methods

Confidence intervals for response rates were calculated using standard techniques.

RESULTS

Patients' characteristics (Table 2)

From March 1986 to September 1988, 34 patients were enrolled by eight institutions. 3 patients with PCR were not

Table 2. Patients' characteristics

		Number of patients
Total no. of patients		34
Non-eligible (patients with PCR at entry)		3
Not evaluable for response		6
Local complications		3
Refused laparotomy		3
Evaluable for toxicity		34
Evaluable for response		25
Median age	58 years (range 45–73)	
Performance status		
0		16
1		9
Response to intravenous cisplatin		
Response		19
Stable disease		4
Progressive disease		1
Not available		1
Previous abdominal radiotherapy		2
Intraperitoneal treatment time		
Treated at second look		14
Treated for relapse disease		11
Residual disease before intraperitoneal cisplatin		
Microscopic disease		8
≤5 mm		8
5 mm < residual disease ≤ 10 mm		9

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eligible, although these patients were taken into account for toxicity analysis. 31 patients were eligible. 6 patients were not evaluable for response but were evaluable for toxicity. 3 of them refused evaluation laparotomy and 3 had incomplete treatment due to excessive toxicity, 1 for obstruction of peritoneal catheter at the second cycle of chemotherapy, 1 for grade 1 peripheral neuropathy plus grade 2 renal toxicity after the fourth cycle, and 1 for staphylococcus peritonitis after the first cycle. 25 patients were fully evaluable.

From the 34 included patients, disease evaluation before intraperitoneal treatment was performed by means of a laparotomy in 33 cases and by laparoscopy in 1 case. 26 patients had a totally implantable system for intraperitoneal perfusion (Port-A-Cath), 4 patients had an external Tenckoff catheter, and 4 patients were treated by other systems (disposable catheters). The catheter was inserted under general anesthesia in 27 cases, and under local anesthesia in 6 cases (1 case unspecified). The mean duration of hospital stay between catheter placement and the first intraperitoneal course was 11 days (range 1–24). All patients had previously received cisplatin or carboplatin, some patients received more than one chemotherapy regimen. 3 patients were treated with monochemotherapy, 1 with cisplatin alone, 2 with carboplatin alone and all other patients had association regimens. In total, 30 patients (88%) received cisplatin, 5 (15%) carboplatin, 31 (91%) cyclophosphamide, 16 (47%) doxorubicin, 8 (23%) hexamethylmelamine, 5 (15%) etoposide and 1 received 5-fluorouracil. 30 patients (88%) were initially stage III, 2 were stage IV, 1 was stage IIb and 1 was stage unknown.

From the 25 fully evaluable patients, median age was 58 (range 45–73), performance status was 0 in 16 patients and 1 in 9 patients (WHO classification). 8 patients (32%) had achieved a complete response after induction of intravenous chemotherapy, but subsequently developed a recurrence after a median delay of 16.7 months (range 4–29), and were treated at that time. 3 patients with partial response after intravenous treatment had a treatment-free interval of 13, 14 and 17 months, respectively, before intraperitoneal therapy. 14 patients were treated at the time of second-look laparotomy: 8 had partial response after induction chemotherapy, 4 had stable disease, 1 had progressive disease, and information for response evaluation was missing for 1 patient. 2 patients had received abdominal radiotherapy at doses of 36 and 22 Gy, respectively. At the time of intraperitoneal chemotherapy, 8 patients (32%) had microscopic disease, 8 (32%) had ≤5 mm residual disease, and 9 (36%) had lesions >5 mm but ≤10 mm. The 25 evaluable patients received a total of 115 courses of therapy. 6 patients were not evaluable for response but were evaluable for toxicity; they received 18 cycles of intraperitoneal chemotherapy. Non-eligible patients received 14 courses.

Response

Evaluation was performed by laparatomy in 17 patients; in the other 8 patients progression was clinically evident during treatment.

There were three PCRs (12%) and one microscopic disease (Table 3), so the overall response rate for evaluable patients was 16% (95% confidence interval, 1.6–30.3%). The residual volume disease before intraperitoneal therapy for the 3 patients with complete response was ≤1 mm, ≤5 mm, and microscopic disease, and the response was assessed after 10, 20 and 20 blind peritoneal biopsies, respectively. The patient who reached microscopic disease had ≤10 mm volume disease. All 4 patients who responded after intraperitoneal cisplatin were responders after induction intravenous chemotherapy; they all received six cycles of intraperitoneal cisplatin, and 3 of them received intravenous sodium thiosulphate.

Table 3. Responders' characteristics

Treatment time	Volume residual disease	No. of cycles with intraperitoneal cisplatin	Response (months)	Number of blind biopsies to assess response
II look	≤1 mm	6 (1 NaTh)	PCR (5)	10
II look	≤5 mm	6 (4 NaTh)	PCR (57+)	20
II look	Mic dis	6	PCR (45+)	20
Relapse*	≤10 mm	6 (3 NaTh)	Mic dis (18)	10

*24 month interval from intravenous chemotherapy. II look, patients treated at the time of second-look laparotomy; Relapse, patient treated for recurrent disease; NaTh, number of cycles with intravenous sodium thiosulphate administration; PCR, pathological complete response; Mic dis, microscopic disease.

Response duration

The duration of the three PCRs was 5, 45+ and 57+ months. The patient with microscopic disease relapsed after 18 months.

Fluid abdominal diffusion

According to protocol and to the total number of intraperitoneally administered cycles, fluid diffusion was studied in 50 of the 78 planned courses (64%). Fluid diffusion was considered good in 44 cycles (56%) and partially defective in six (8%). 2 patients with partially defective distribution at the first cycle (1 with a pelvic defect, another with a defect in the right part of the abdomen) reached a good fluid distribution at the third cycle. 3 patients with initially good diffusion had partially defective fluid distribution at the third cycle, and these 5 patients progressed.

Toxicity

One hundred and forty-seven courses were analysed for toxicity in 34 patients.

Systemic toxicity (*Table* 4). No grade 4 systemic toxicity was observed.

Haematological toxicity. Haematological toxicity was mild: WHO grade 3 toxicity was present in only four courses for

Table 4. Systemic toxicity

	WHO grade*			
	0	1	2	3
147 evaluable cycles				
Haemoglobin	79 (54%)	48 (33%)	16 (11%)	4 (3)
Leucocytes	77 (52%)	56 (38%)	13 (9%)	1 (0.7)
Platelets	135 (92%)	6 (4%)	5 (3%)	1 (0.7)
Vomiting	3 (2%)	21 (14%)	76 (52%)	47 (32%)
Diarrhoea	133 (90%)	13 (9%)	0	1 (0.7)
34 evaluable patients				
Renal toxicity	22 (65%)	8 (24%)	4 (12%)	0
Neuropathy	28 (82%)	6 (18%)		

*No grade 4 toxicity was observed.

haemoglobin, one course for leucocytes, and one course for platelets. 6 patients received sodium thiosulphate for haematological protection, which was for leucopenia in all cases.

Non-haematological toxicity. Grades 1 and 2 vomiting were observed in 97 courses (66%), and grade 3 in 47 courses (32%). Grade 1 diarrhoea occurred in 13 courses (9%), and grade 3 in one. Grade 1 and 2 renal toxicity occurred in 12 patients, 8 of whom received sodium thiosulphate for intentional renal protective effect. Grade 1 peripheral neuropathy was observed in 6 patients.

Sodium thiosulphate protective effect

14 patients received sodium thiosulphate with the intention of providing a protective effect. 3 patients did not present any criteria for receiving sodium thiosulphate and were not evaluable for protective effect analysis. 3 patients were treated for haematological toxicity (WBC $\leq 3.0 \times 10^9$/l); 5 patients were treated for renal toxicity (25% increased basal creatinine level) and 3 patients were treated for both haematological and renal toxicity. All received identical doses of cisplatin.

8 patients with renal toxicity had a mean increased creatinine level, before sodium thiosulphate introduction, of 65% (range 25–149%). After sodium thiosulphate, the subsequent mean increased creatinine level was 15% (range 0–73%); for these 8 patients, a total of 18 courses of chemotherapy were administered without sodium thiosulphate and 18 courses were administered with sodium thiosulphate. The results indicate a protective renal effect of sodium thiosulphate (Table 5).

6 patients with haematological toxicity had a mean WBC nadir of 2.9×10^9/l at the last chemotherapy course preceding sodium thiosulphate introduction, and a mean WBC nadir of 3.9×10^9/l at the following course in which patients received additional intravenous sodium thiosulphate perfusion. The results indicate a protective haematological effect of sodium thiosulphate (Table 6).

Table 5. Renal protective effect of intravenous sodium thiosulphate: creatinine levels before and after introduction of intravenous sodium thiosulphate

		Before sodium thiosulphate		After intravenous thiosulphate	
Patient number	Initial creatinine level* (μmol/l)	No. of intra-peritoneal courses	Last creatinine level† (μmol/l)(%)	No. of intra-peritoneal courses	Last creatinine level‡ (μmol/l)(%)
1	103	3	140 (45%)	3	178 (19%)
3	120	2	169 (41%)	4	201 (19%)
4	88	3	130 (47%)	3	144 (11%)
12	105	1	133 (25%)	1	134 (1%)
27	103	1	256 (149%)	1	442 (73%)
28	92	1	123 (34%)	1	118 (0%)
30	90	5	165 (83%)	1	166 (0%)
31	133	2	276 (100%)	2	237 (0%)

*Creatinine level at entry into the study. †Last creatinine level before intravenous sodium thiosulphate administration. Increased percentage from basal level. ‡Creatinine level when the patient completed the study after thiosulphate administration. Increased percentage from creatinine level before sodium thiosulphate administration.

Table 6. Haematological protective effect of intravenous sodium thiosulphate

	WBC nadir ($\times 10^9$/l)	
Patient number	At the final chemotherapy course before intravenous sodium thiosulphate	At the first chemotherapy course with intravenous thiosulphate
1	3.0	4.7
3	2.8	4.6
4	3.0	3.2
25	2.5	4.6
26	3.0	4.1
32	2.9	2.4
Mean	2.9	3.9

The dose of intraperitoneal cisplatin remained identical in all cases.

Local toxicity

Immediate postoperative complications at entry were observed in 9 patients, as detailed in Table 7. A surgical procedure to remove the catheter was necessary in 4 of these cases.

One hundred and forty-seven cycles of chemotherapy were evaluable for local toxicity, and as indicated in Table 7, local toxicity was observed in 5 patients. Abdominal discomfort was present in 32 cycles (22%), partial outflow obstruction in 48 cycles (33%), total outflow obstruction in 58 cycles (39%), partial inflow obstruction in nine cycles (6%), and total obstruction in one cycle. In 2 patients, who had also received abdominal radiotherapy, no particular complications were observed: 1 patient progressed after one uncomplicated course, and initial abdominal fluid diffusion was good; the other patient received four cycles with mild pain at the second cycle; abdominal fluid diffusion was good at the first and third courses.

During the time of intraperitoneal treatment, 4 patients had surgical procedures for catheter-related complications: in 1 patient with discomfort the Tenckoff catheter was changed to a Port-A-Cath under local anesthesia at the fifth cycle; in 1 patient with abdominal discomfort and fever, the Port-A-Cath was removed and treatment pursued with blind abdominal punc-

Table 7. Local side-effects (34 evaluable patients)

	No. of patients
Immediate postoperative complications at entry	
Fever	1
Bleeding	1
Outflow catheter obstruction	3
Leakage of fluid	2
Catheter perforation	1
Reservoir disconnection	1
Surgical procedure for catheter removal	4
Local toxicity during treatment	
Infectious peritonitis	2
Wound infection	1
Bleeding	2
Surgical procedure for catheter-related complications	4

tures. 1 patient was operated upon in emergency for acute intestinal occlusion caused by intestinal injury at the site of the peritoneal catheter tip; in the last patient with total inflow obstruction, a catheter replacement was performed under general anesthesia and laparoscopic control—this patient died 24 h later with toxic stomacal dilation and severe vomiting. Autopsy showed subileus and progressive tumour.

DISCUSSION

Intraperitoneal chemotherapy is an innovative approach, based on the pharmacological advantage for drugs instillated into the abdominal cavity, where the concentration reached is many times higher than that in the plasma; the rationale is the potential to translate this advantage into an improved therapeutic index. Another advantage for intraperitoneal therapy is the use of intravenous neutralising agent which may reduce systemic toxicity, such as for cisplatin.

When we initiated our trial in 1985, the results of several pilot and phase II studies had been published, and interesting response rates had been observed, especially in minimal disease. However, survival benefit was not evident and phase III studies appeared necessary to define the role for intraperitoneal therapy precisely. Before starting such a comparative trial, we performed a phase II study to become familiar with the technical administration of peritoneal cisplatin in a multicentre setting, to determine the response rate for lesions ≤ 1 cm, and to define the side-effects of such treatment.

In the current study, 6/31 (19%) eligible patients were not evaluable for response, 3 because of local complications during intraperitoneal chemotherapy, and the other 3 refused evaluation laparotomy. This number of non-evaluable patients is high, reflecting both the difficulty of evaluating tumoral response after chemotherapy in ovarian carcinoma with minimal residual disease, and technical difficulties in administering cisplatin by the intraperitoneal route. Local side-effects related to intraperitoneal access observed in our study are very similar to those observed by other authors [11]: infections related to implanted material, organ injuries related to the abdominal catheter and numerous surgical manipulations required by catheter dysfunctions. 1 patient died after a surgical replacement procedure of the peritoneal catheter.

The 3 complete responses were observed in patients treated at the time of second-look laparotomy after partial response to induction intravenous chemotherapy. The continuation of intravenous chemotherapy for patients in that situation is unlikely to achieve a complete response [12], and these patients would be considered as good candidates for intraperitoneal chemotherapy. These data were confirmed by Piver [13] who observed five PCRs from 31 patients with residual macroscopic disease, after an intravenous cisplatin-based chemotherapy programme. All responders had residual disease <1 cm and responded previously to intravenous cisplatin. The intraperitoneal treatment was a combination of cisplatin, cytarabine and bleomycin with intravenous thiosulphate perfusion. It was concluded that this association would probably not be better than cisplatin alone without sodium thiosulphate rescue.

Nephrotoxicity is clearly reduced when thiosulphate is administered concurrently with peritoneal cisplatin [14]: sodium thiosulphate reacts with cisplatin, and forms a covalent complex that does not generate toxicity for either normal or malignant tissues. Although the rate of reaction between thiosulphate and cisplatin is very low in the plasma, it is quite rapid in the tubular urine and sodium thiosulphate is concentrated 25-fold in the kidney [15]. All these data indicate that cisplatin is neutralised locally in the kidney. Howell has observed that thiosulphate reduces the degree of thrombocytopenia [14], although the mechanism of this protective effect remains unclear.

We confirmed a protective effect of intravenous sodium thiosulphate for cisplatin-induced renal toxicity, and our results also indicate that sodium thiosulphate reduces neutropenia. Three responders received sodium thiosulphate after the appearance of toxicity, suggesting that the effectiveness of intraperitoneal cisplatin may not be neutralised by sodium thiosulphate.

In conclusion, the results of this study indicate that intraperitoneal cisplatinum is active in the treatment of small, abdominal, residual ovarian carcinoma lesions in pretreated patients and we recommend systemic protection with intravenous sodium thiosulphate, if renal or haematological toxicity appears during treatment. We have demonstrated the feasibility of a multicentric study, and a prospective randomised study has been initiated to further assess the role of four cycles of intraperitoneal cisplatin in patients who reached a PCR after intravenous platinum-based chemotherapy. The eventual benefit observed in such a trial will have to be balanced with side-effects due to intraperitoneal drug administration.

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